TELECON MINUTES

MEETING DATE: January 30, 2002 **TIME:** 08:30 a.m. **LOCATION:** Corp S300

NDA 21-042/S-007, 012
NDA 21-052/S-004, 007

Telecon Request Date: December 19, 2001
Telecon Cancelled by Sponsor: January 07, 2002
Telecon Rescheduled: January 17, 2002

DRUG: Vioxx (rofecoxib) Tablets 12.5 mg, 25 mg, 50 mg
Vioxx (rofecoxib) Suspension 12.5 mg/5 mL, 25mg/5 mL

SPONSOR/APPLICANT: Merck Research Laboratories

TYPE of TELECON: Labeling Negotiations

FDA PARTICIPANTS:	**Division of Anti-Inflammatory, Analgesics, & Ophthalmic Drug Product**
Jonca C. Bull, MD	Acting Director, Deputy Director, Office of Drug Evaluation V
Larry Goldkind, MD	Deputy Division Director
James Witter, MD, Ph.D.	Acting Medical Team Leader
Maria L. Villalba, MD	Medical Reviewer
Joel Schiffenbauer, MD	Medical Reviewer
Stan Lin, Ph.D.	Biostatistics Team Leader
Carmen DeBellas, R.Ph.	Chief, Project Management Staff
Barbara Gould	Project Manager
Robert Temple, MD	Director, Office of Medical Policy
Laura Governale	Project Manager, Office of Medical Policy, DDMAC

INDUSTRY PARTICIPANTS:	**Merck Research Laboratories**
Dr. Bonnie Goldmann	Regulatory Affairs
Dr. Robert Silverman	Regulatory Affairs
Dr. Ned Braunstein	Regulatory Affairs
Dr. Diane Benezra	Regulatory Affairs
Ms. Dawn Chitty	Regulatory Affairs
Dr. Alise Reicin	Clinical Research and Sciences
Dr. Kenneth Truitt	Clinical Research and Sciences
Dr. Thomas Simon	Clinical Research and Sciences
Dr. Barry Gertz	Clinical Research and Sciences
Dr. Deborah Shapiro	Clinical Biostatistics
Mr. James Bolognese	Clinical Biostatistics
Dr. Leonard Oppenheimer	Clinical Biostatistics
Dr. Douglas Watson	Epidemiology
Dr. Harry Guess	Epidemiology
Dr. Thomas Bold	Worldwide Product Safety and Epidemiology
Ms. Linda Hostelley	Worldwide Product Safety and Epidemiology
Dr. Douglas Greene	Clinical Scientific and Product Development

Dr. Peter Kim — Research & Development
Mr. Thomas Casola — Office of Medical/Legal

BACKGROUND INFORMATION:
Reference is made to the above cited supplemental New Drug Applications (sNDA) submitted as electronic archives on June 29, 2000 which provided for changes to the labeling as a result of the VIOXX™ Gastrointestinal Outcomes Research (**VIGOR**) study. Reference is also made to an October 15, 2001 letter from the Agency to Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. containing the Agency's labeling proposal for the VIGOR sNDA; MRL's response to Agency's labeling proposal submitted on November 6, 2001; a telephone conversation between Dr. Larry Goldkind (FDA) and Dr. Robert E. Silverman (MRL) on November 21, 2001 during which the VIGOR labeling was discussed; a submission dated December 5, 2001 containing MRL's updated labeling proposal; and a FDA fax dated December 21, 2001 containing proposed labeling to be discussed at an upcoming teleconference scheduled for January 9, 2002.

At Merck's request the teleconference scheduled for January 09, 2002 was cancelled and rescheduled on January 17, 2002 for January 30, 2002, when Dr. Robert Temple would be available. On January 29, 2002 a list of FDA tentative participant, a revised label, and agenda was forwarded to MRL that would be basis for teleconference on January 30, 2002.

DISCUSSION:
The teleconference began with opening remarks by Dr. Jonca Bull. Dr. Bull acknowledged that the deletion of information regarding GI warning was an oversight. Both parties agreed that there is new safety information that needs to be communicated based findings in the VIGOR studies. Dr. Bull summarized by stating that the way to move forward in the interim clearly is by indicating what prescribers need to convey to their patients.

Dr. Goldmann stated that it would help Merck in understanding what key points the FDA felt needed to be communicated in the Vioxx label.

MERCK: VIGOR was primarily designed to evaluate GI outcomes. Other safety endpoints are always included in all Merck trials and should not be as prominent as the primary endpoint. The Agency is putting more weight on the non-GI findings than on the positive GI findings of the study. Edema and hypertension are known effects of the NSAID class.

FDA: The goal of the Division is not to detract from the GI endpoints. However, the Division views the overall safety data and CV data, particularly CV/thrombotic events in VIGOR as relevant and provide context for the GI results. We propose a single table (similar to the current NSABP-1 Trial in the Nolvadex label). More than one table in the clinical section of the label might also be acceptable.

MERCK: CV data in VIGOR is not supported in Alzheimer's studies. The S including a paragraph about the Alzheimer's study and also requeste dosage section: "*50 mg not to be used past 5 days for acute pain*".

FDA: The Division has concerns over inclusion of prematurely completed studies and studies in progress. The complete report of these studies has not been submitted for review and one of the studies is still ongoing. We anticipate future dialogue regarding the Alzheimer's clinical studies.

MERCK: Would early termination of the ongoing study and submission of the Alzheimer's data suffice to be included in present label? Also could the meta-analysis of CV/thrombotic events in the VIOXX program, and/or analysis of phase IIbIII OA studies be included.

FDA: You may consider a labeling supplement when studies are completed. We do not advise you to stop the ongoing Alzheimer's study. Meta-analysis of studies of varying duration, dose, and indication are inherently difficult to interpret.

Meta-analysis has been discussed at the Arthritis Advisory Committee, at the center level and with biostatisticians in the Agency. The level of confidence with meta-analysis does not rise to the level of a prospectively designed, well-controlled, study of adequate duration, and size for a given dose.

MERCK: Merck proposed to send clarification of numbers where there seems to be misinterpretation of the data. The Sponsor requested clarification as to why information has been struck from label. Suggestion was make to the Agency to look again at the January 08, 2002 label proposal. Merck would like to go through the label to find why certain information has bee removed.

ACTION ITEMS:

1. FDA will re-review Merck's January 08, 2002 proposed label and future agendas will include further clarification of the Division's labeling concerns.
2. Agreed to reconvene in one week for further label discussions.
3. Minutes of the teleconference will be conveyed within 30 days.

Barbara Gould Date
Project Manager

Concurrence Chair:

Lawrence Goldkind, MD Date
Deputy Division Director

Initialed by:

TELECON MINUTES

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/s/

Lawrence Goldkind
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TELECON MINUTES

MEETING DATE: February 08, 2002 **TIME:** 1:30 P.M. **LOCATION:** Corp S300

NDA 21-042/S-007, 012
NDA 21-052/S-004, 007

DRUG: Vioxx (rofecoxib) Tablets 12.5 mg, 25 mg, 50 mg
Vioxx (rofecoxib) Suspension 12.5 mg/5 mL, 25mg/5 mL

SPONSOR/APPLICANT: Merck Research Laboratories

TYPE of TELECON: Labeling Negotiations

FDA PARTICIPANTS:	**Division of Anti-Inflammatory, Analgesics, & Ophthalmic Drug Product**
Jonca C. Bull, MD	Acting Director, Deputy Director, Office of Drug Evaluation V
Larry Goldkind, MD	Deputy Division Director
James Witter, MD, Ph.D.	Acting Medical Team Leader
Maria L. Villalba, MD	Medical Reviewer
Joel Schiffenbauer, MD	Medical Reviewer
Lisa Hubbard, RPh.	Labeling Reviewer
Barbara Gould	Project Manager

INDUSTRY PARTICIPANTS:	**Merck Research Laboratories**
Dr. Bonnie Goldmann	Regulatory Affairs
Dr. Robert Silverman	Regulatory Affairs
Dr. Ned Braunstein	Regulatory Affairs
Dr. Diane Benezra	Regulatory Affairs
Ms. Dawn Chitty	Regulatory Affairs
Dr. Alise Reicin	Clinical Research and Sciences
Dr. Kenneth Truitt	Clinical Research and Sciences
Dr. Thomas Simon	Clinical Research and Sciences
Dr. Barry Gertz	Clinical Research and Sciences
Dr. Deborah Shapiro	Clinical Biostatistics
Mr. James Bolognese	Clinical Biostatistics
Dr. Leonard Oppenheimer	Clinical Biostatistics
Dr. Douglas Watson	Epidemiology
Dr. Harry Guess	Epidemiology
Dr. Thomas Bold	Worldwide Product Safety and Epidemiology
Ms. Linda Hostelley	Worldwide Product Safety and Epidemiology
Dr. Douglas Greene	Clinical Scientific and Product Development
Dr. Peter Kim	Research & Development
Mr. Thomas Casola	Office of Medical/Legal

DISCUSSION:

FDA: The cardiovascular (CV) findings in VIGOR are clinically relevant and need to be in the label. Results are an important part of the overall comparative safety.

MERCK: Agreed that CV thrombotic events and MI data from VIGOR are appropriate for the label but needed further discussion about location. Proposed to include absence of CV signal in OA phase IIbIII studies.

FDA: Lack of differences seen in a meta-analysis of phase IIbIII studies are not adequately informative to warrant inclusion in the label. Phase IIbIII studies included trials of different design, size and duration, using different doses of VIOXX and different comparators.

Regarding low dose ASA co-administration: Statements suggesting that there is adequate information on con-administration of ASA and VIOXX are not supported by data. Six to 12 week studies (ADVANTAGE, 085 and 090) did not support an affirmative statement regarding safety of co-administration. (See Medical Officer Review of Complete Response to Approvable letter dated 11/28/2001 and the original NDA 21-042 GI review and M.O. Safety reviews.

MERCK: Disagreed with FDA proposed post-marketing statements regarding fluid retention, edema, hypertension and renal events, as well as mention of post-marketing events in the geriatric portion of the label. All these events are covered by the NSAID class labeling.

ACTION ITEMS:

1. Agreed to reconvene for further label discussions.
2. Minutes of the teleconference will be conveyed within 30 days.

Barbara Gould Date
Project Manager

Concurrence Chair:

Lawrence Goldkind, MD Date
Deputy Division Director

Initialed by:

TELECON MINUTES

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/s/

Lawrence Goldkind
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TELECON MINUTES

MEETING DATE: February 20, 2002 **TIME:** 1:30 P.M. **LOCATION:** Corp N351

NDA 21-042/S-007, 012
NDA 21-052/S-004, 007

DRUG: Vioxx (rofecoxib) Tablets 12.5 mg, 25 mg, 50 mg
Vioxx (rofecoxib) Suspension 12.5 mg/5 mL, 25mg/5 mL

SPONSOR/APPLICANT: Merck Research Laboratories

TYPE of TELECON: Labeling Negotiations

FDA PARTICIPANTS:	**Division of Anti-Inflammatory, Analgesics, & Ophthalmic Drug Product**
Jonca C. Bull, MD	Acting Director, Deputy Director, Office of Drug Evaluation V
Larry Goldkind, MD	Deputy Division Director
James Witter, MD, Ph.D.	Acting Medical Team Leader
Maria L. Villalba, MD	Medical Reviewer
Joel Schiffenbauer, MD	Medical Reviewer
Lisa Hubbard, RPh.	Labeling Reviewer
Barbara Gould	Project Manager

INDUSTRY PARTICIPANTS:	**Merck Research Laboratories**
Dr. Bonnie Goldmann	Regulatory Affairs
Dr. Robert Silverman	Regulatory Affairs
Dr. Ned Braunstein	Regulatory Affairs
Dr. Diane Benezra	Regulatory Affairs
Ms. Dawn Chitty	Regulatory Affairs
Dr. Alise Reicin	Clinical Research and Sciences
Dr. Kenneth Truitt	Clinical Research and Sciences
Dr. Thomas Simon	Clinical Research and Sciences
Dr. Barry Gertz	Clinical Research and Sciences
Dr. Deborah Shapiro	Clinical Biostatistics
Mr. James Bolognese	Clinical Biostatistics
Dr. Leonard Oppenheimer	Clinical Biostatistics
Dr. Douglas Watson	Epidemiology
Dr. Harry Guess	Epidemiology
Dr. Thomas Bold	Worldwide Product Safety and Epidemiology
Ms. Linda Hostelley	Worldwide Product Safety and Epidemiology
Dr. Douglas Greene	Clinical Scientific and Product Development
Dr. Peter Kim	Research & Development
Mr. Thomas Casola	Office of Medical/Legal

DISCUSSION:

Merck draft of 15 Feb 2002 with proposals resulting from 08 Feb 2002 FDA teleconference. Main issues for discussion:

1. FDA noted that we have asked Merck to provide Kaplan Meier rates of GI and CV thrombotic events but still have not received that information. Rates per 100-patient-years do not give same information as cumulative data. Cumulative rates include the concept of time dependence. We continue to believe that KM cumulative rates are most informative for prescribers.

   MERCK expressed concern about cumulative rates.

2. FDA would like to see clearly in the label that ASA was not allowed under VIGOR study design.

   MERCK agreed.

3. FDA suggested that redundancy of tables and figures reflecting endoscopic studies should be consolidated.

   MERCK agreed.

4. MERCK strongly feels that postmarketing information about fluid retention, hypertension, edema and renal events should require labeling supplement across all NSAIDs.

5. At an earlier teleconference Merck had proposed that CV data from three Alzheimer's studies be included in the label. The Agency was concerned that full report of these studies had not been reviewed by the Agency. Additionally, one of the studies had been prematurely terminated after 5 months (#126) and one study was still ongoing and blinded (#078).

   After MO review of available data on March 12, 2002 and internal discussion it was felt that inclusion of CV thrombotic events from the two long-term placebo controlled Alzheimer's studies (study 078 and 091, with a median duration of 14 months) would provide relevant information on clinically approved doses of VIOXX versus placebo. CV deaths should also be included.

6. FDA requested that the incidence of hypertension with VIOXX 25 mg in RA efficacy database be included in the label. The incidence of hypertension in the current VIOXX label reflects a combination of the 12.5 and 25 mg dose in 6-weeks to 6-month OA studies (<3%). In the RA studies the incidence of hypertension was 10 % in studies of 3 months to one year with the 25 mg dose and 4.7% in the Naproxen treated group.

ACTION ITEMS:

1. The Division will continue to discuss with Center statisticians the statistical presentation of data for CV and GI events in the label (Kaplan Meier vs. event rate per 100 patient years).
2. Agreed to reconvene for further label discussions.
3. Minutes of the teleconference will be conveyed within 30 days.

Barbara Gould Date
Project Manager

Concurrence Chair:

Lawrence Goldkind, MD Date
Deputy Division Director

Initialed by: LVillalba/
LGoldkind/
JBull

TELECON MINUTES

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Lawrence Goldkind
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TELECON MINUTES

MEETING DATE: March 07, 2002 **TIME:** 2:00 P.M. **LOCATION:** Corp N351

NDA 21-042/S-007, 012
NDA 21-052/S-004, 007

DRUG: Vioxx (rofecoxib) Tablets 12.5 mg, 25 mg, 50 mg
Vioxx (rofecoxib) Suspension 12.5 mg/5 mL, 25mg/5 mL

SPONSOR/APPLICANT: Merck Research Laboratories

TYPE of TELECON: Labeling Negotiations

FDA PARTICIPANTS:	**Division of Anti-Inflammatory, Analgesics, & Ophthalmic Drug Product**
Jonca C. Bull, MD	Acting Director, Deputy Director, Office of Drug Evaluation V
Larry Goldkind, MD	Deputy Division Director
Maria L. Villalba, MD	Medical Reviewer
Stan Lin, Ph.D.	Biostatistics Team Leader
Lisa Hubbard, RPh.	Labeling Reviewer
Barbara Gould	Project Manager
Robert O'Neill, Ph.D	Director, Office of Biostatistics (Joined the teleconference at 3:40 P.M.)

INDUSTRY PARTICIPANTS:	**Merck Research Laboratories**
Dr. Bonnie Goldmann	Regulatory Affairs
Dr. Robert Silverman	Regulatory Affairs
Dr. Ned Braunstein	Regulatory Affairs
Dr. Diane Benezra	Regulatory Affairs
Ms. Dawn Chitty	Regulatory Affairs
Dr. Alise Reicin	Clinical Research and Sciences
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Dr. Thomas Bold	Worldwide Product Safety and Epidemiology
Ms. Linda Hostelley	Worldwide Product Safety and Epidemiology
Dr. Douglas Greene	Clinical Scientific and Product Development
Dr. Peter Kim	Research & Development
Mr. Thomas Casola	Office of Medical/Legal

DISCUSSION:

Merck draft of 15 Feb 2002 with proposals resulting from 20 Feb 2002 FDA teleconference

FDA The Division has had internal discussions with statisticians from the Division and the Center regarding how safety data are most appropriately displayed in the context of cumulative exposure. The best way to display the data is the Kaplan Meier curve. FDA is not comfortable with Merck's conclusion that the hazard rate of CV thrombotic events is constant over time. The issue of potential change in hazard rate over time is not addressed in a crude rate or in event per 100 patient-years rate. Precedents for of including KM curves in labels exist.

MERCK: The K-M curve has optical illusion and looks like something is happening that is not happening (looks like a bump in curve that is not accurately representing the data). Several statistical tests did not show statistically significant differences in hazard rates over time.

FDA: Failure to show a statistical significant difference does not prove absence of change in hazard rate over time. K-M statistics are standard to depict effects and outcome. K-M plot does portray rates over time information.

(Note: The time devoted to how to best display cardiovascular safety from VIGOR reflects how important the Agency considers the topic of clear labeling of safety information).

ACTION ITEMS:

1. The Division will arrange a meeting with Center statisticians to discuss statistical presentation of data for CV and GI events in the label.
2. Agreed to reconvene for further label discussions.
3. Minutes of the teleconference will be conveyed within 30 days.

Barbara Gould Date
Project Manager

Concurrence Chair:

Lawrence Goldkind, MD Date
Deputy Division Director

Initial by: LVillalba/
LStan/
RO'Neill/
LGoldkind/
JBull/

TELECON MINUTES

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/s/

Lawrence Goldkind
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TELECON MINUTES

TELECON DATE: March 20, 2002 **TIME:** 10:00 a.m. **LOCATION:** Corp S314

NDA 21-042/S-007, 012
NDA 21-052/S-004, 007

DRUG: Vioxx (rofecoxib) Tablets 12.5 mg, 25 mg, 50 mg
Vioxx (rofecoxib) Suspension 12.5 mg/5 mL, 25mg/5 mL

SPONSOR/APPLICANT: Merck Research Laboratories

TYPE of TELECON: Labeling Negotiations

FDA PARTICIPANTS:	**Division of Anti-Inflammatory, Analgesics, & Ophthalmic Drug Product**
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Larry Goldkind, MD	Deputy Division Director
Maria L. Villalba, MD	Medical Reviewer
Stan Lin, Ph.D.	Biostatistics Team Leader
Lisa Hubbard, RPh	Labeling Reviewer
Barbara Gould	Project Manager
Robert O'Neill, Ph.D.	Director, Office of Biostatistics

INDUSTRY PARTICIPANTS:	**Merck Research Laboratories**
Dr. Bonnie Goldmann	Regulatory Affairs
Dr. Robert Silverman	Regulatory Affairs
Dr. Ned Braunstein	Regulatory Affairs
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Dr. Douglas Greene	Clinical Scientific and Product Development
Dr. Peter Kim	Research & Development
Mr. Thomas Casola	Office of Medical/Legal

DISCUSSION:

The Division position is that the best way to display cardiovascular data from VIGOR in the label is to include a representation of the event rates over time of study as in the Kaplan Meier cumulative curve of adjudicated cardiovascular thrombotic events, and an additional table that summarizes important information on relative risk estimates, events and numbers of persons in trial.

The Division does not agree with the display of the CV data as events per 100 patient years because relative risk is presented as a single number which, by its very definition, assumes that the hazard rate is constant over the 12 months of the study (an average over the 11 month period that does not reflect different risk over time). Our analyses strongly suggest that the data does not support this assumption and that, in contrast, there is considerable evidence to suggest that the hazard rate is not constant and that therefor no single incidence rate metric adequately summarizes the incidence rate over time.

Merck does not want the graph of the cumulative Kaplan Meier curve of cardiovascular thrombotic events because the graphic display of the time curve of cumulative risk makes it look as if the hazard rate changed over time, when in fact, their multiple analyses demonstrate that it is not the case.

FDA does not agree with Merck's conclusions. Failure to demonstrate a statistically significant difference does not prove that there is no difference in hazard rates over time. Since VIGOR was not specifically designed and adequately powered to show statistically significant differences in hazard rates of CV events, the number of observed events, though pictorially consistent with an increasing hazard rate, does not allow for demonstrating statistically significant evidence for an increasing hazard rate for the adjudicated CV events using available methodology that is recognized as having low power to do so. This does not mean that the lack of evidence for an increasing hazard rate is adequately better supported by the data to conclude that the hazard rate is constant.

Statistical analyses of cardiovascular thrombotic events done by Dr. Huque (March 14, 2002) suggest that the relative risk of developing cardiovascular thrombotic events for VIOXX relative to naproxen is not constant over time, and that it is higher after 8 months. In particular, the estimated hazard rate of adjudicated cardiovascular thrombotic events over the 0-4, 4-8 and 8-12 month periods were 1.36 %, 1.16% and 3.35% for VIOXX and 0.73%, 058% and 0.84% for naproxen, respectively. Table 2. of Dr. Huque's review shows all investigator reported serious cardiovascular thrombotic events. Analyses of this dataset are entirely consistent with the analyses of adjudicated events, and because of the larger number of numerator events, does illustrate non-overlapping confidence intervals for Vioxx when comparing the 0-4 month interval with the 8-12 month interval.

(Of note, the memo submitted by Dr. Huque had typographical errors in Table 1. (number of adjudicated cardiovascular thrombotic events for naproxen). The table lists 14, 12 and 6 instead of 9, 6 and 4 (for the number of events) for the 1-4, 4-8 and 8-12 month periods. However, the statistical analyses and calculations of hazard rates and relative risks were done with the correct numbers.and the results in table 1 are correct). Merck is aware that this was a typographical error in the materials sent to them prior to the telephone conference call.

Merck's proposal to display a table of cumulative incidence rate for all adjudicated CV thrombotic events (along with relative risk, 95% CI and p value) and number of events (without cumulative rates but with p values for all cardiac events and MI), is better than their proposal for the display of rates per 100 patient years but still is not the optimal way to present the data.

Of note, the cumulative incidence rate of adjudicated CV thrombotic events is 1.8 % and 0.6 % for the VIOXX and naproxen groups respectively. Taking the ratio of these two cumulative incidence rates provides a 3 fold increase in risk, ie relative risk. However, the estimated relative risk based on the COX proportional hazard rate analysis is 2.37. The reason for this discrepancy is that the Cox models is an average hazard rate over the 12 months and since the rate is very suggestive of increasing in the latter part of 12 months, these two estimates do not agree. That is the motivation for presenting the Kaplan Meier total curves over 12 month time period.

Merck strongly disagrees with the display of the Kaplan Meier curve. Merck was encouraged to provide different ways of presenting these cardiovascular data for agency review. The Division expressed an understanding that the transient decrease in event rate at the 6-7 month point gives an exaggerated visual appearance to the K-M curve. However, changes in rate over time must be addressed in labeling.

ACTION ITEMS:

1. The Division will consider a predecisional meeting to discuss statistical presentation of data in the label.
2. Merck will submit updated draft label and Patient Product Information (PPI) for the VIOXX™ VIGOR sNDA based on discussions held on March 20, 2002.
3. Minutes of the teleconference will be conveyed within 30 days.

Barbara Gould Date
Project Manager

Concurrence Chair:

Lawrence Goldkind, MD Date
Deputy Division Director

Attachments:

1. March 14, 2002 Memorandum of Consultation from Dr. Huque
2. Addendum to the Memorandum of Consultation of March 14, 2002

Initialed by: ONeillR/*22-Mar-02*

TELECON MINUTES